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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,137	02/15/2002	Browning Jeffrey	A080 US	2907

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,137	JEFFREY ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,20,25-27,29,32,33,35,36,38-40,42,43,45-47,49,50 and 52-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20,25-27,29,32,33,35,36,38-40,42,43,45-47,49,50 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-14-06 has been entered.

Claims 19, 20, 25-27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50 and 52-56 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Information Disclosure Statement

The information disclosure statement filed 6-14-06 has been considered and an initialed copy is enclosed.

Rejections Withdrawn

The objection to claim 19 and all dependent claims is withdrawn. BCMA and BAFF are not defined in the independent claims under examination.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter is withdrawn based on Amendments to the claims.

The rejection of claims 19-21, 25-52 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn based on the amendments and cancellation of the claims.

The rejection of claims 19-21, 25-52 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn based on the amendment to the claims.

The rejection of claims 19, 27-34, 36-37, 39-41, 43-44, 46-48 and 50-51 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the consideration of the written description guidelines Example 14 as the claims recite structure and function.

Rejections Maintained

Priority

Applicants argue that they are entitled to the priority of 60/149,378 filed August 17, 1999. Applicants present arguments providing for specific passages of the provisional document. These passages set forth the now claimed invention with the exception of page 6, lines 8-111 for a BAFF-R-Fc construct comprising nucleic acids 1-153 of BAFF-R. This is not persuasive for the claimed invention in the instant application. The specie described comprises residues 1-51 as a fusion protein with an Fc domain of a particular immunoglobulin. The entire provisional specification is drawn to residues 1-52 of BAFF-R and variants thereof. Therefore, the instant claims could not have been entered into the provisional document without engendering a new matter rejection because it creates a new subgenus that lacks descriptive support therein. It cannot be said that a subgenus is necessarily described by a genus encompassing it (95% identical to residues 1-52) and a species upon which it reads (an Fc fusion protein comprising residues 1-51). See *In re Smith* 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Further, in order to be accorded the filing date of a provisional document under 119(e), the document must comply with 35 USC 112, first paragraph. Applicants argue that the provisional document is enabled because the specification viewed in light of the

state of the art at the time of filing does establish a nexus between *in vitro* and *in vivo* activity. Applicants assert that the examiner has provided no reason to doubt and that the in vitro example constitutes a "working example" and only a reasonable correlation with in vivo is necessary. This is not persuasive. The immunoprecipitation example of the provisional cannot be construed as a pharmaceutical use or have any bearing on B-cell growth or immunoglobulin production. The claimed invention requires an amount effective to inhibit B-cell growth or immunoglobulin production. There is no working example that provides for this activity *in vitro*. Applicants were not in possession of a working example of the claimed invention *in vitro* as asserted. Applicants argue that the skilled artisan would consider the state of the art as provided by Schneider et al, Moreland et al, Examples 1-4 of binding and immunoprecipitation would lead the skilled artisan to conclude that the claimed pharmaceutical compositions could be used *in vivo* without undue experimentation. This is not persuasive because BAFF is a co-stimulator and not the only cytokine available *in vivo* to stimulate B-cell proliferation and immunoglobulin secretion and not the only cytokine in the process. APRIL was also well known in the art to provide for B and T cell proliferation (see WO 99/12965 published 3-18-1999). Mayer et al (Clinical Immunology and Immunopathology 61(2 p. 2):S28-S36, 1991) teaches that the control of B-cell proliferation, maturation and immunoglobulin secretion is complex and controlled at many points by different cytokines all of which would be expected to be present *in vivo*. Schneider et al as cited by Applicants indicate that other ligand/receptor pairs play an important role in B cell survival, proliferation, Ig isotype switch and differentiation (CD40L) and OX40L is necessary for the differentiation of activated B cells into high Ig-producing cells (see page 1747-8, paragraph bridging columns 2-1 respectively). The tumor necrosis factor family of ligands and the counter receptors are known to be among the most pleiotropic cytokines/receptor pairs, inducing a large number of cellular responses, including cell proliferation, cytotoxicity, anti-viral activity, immunoregulatory activities etc. Schneider et al also teaches that the ligand cytokine BAFF is different from other

TNF family members active in the immune response (page 1753, column 2). Therfore, the ligand/receptor pair differs functionally than those other TNF related ligand/receptor pairs that also function in the immune response. The skilled artisan in the area of immunology would immediately recognize the high complexity of the cytokine networks that provide for B cell proliferation, differentiation, maturation and immunoglobulin secretion. Given this *in vivo* complexity of cytokine control of an immune response and that all cytokines/receptor pairs would be expected by the skilled artisan to be active in vivo, one skilled in the art could not predict the *in vitro* or *in vivo* effect of the claimed BMCA (BAFF-R) fragment or 95% variant. Further, it is noted that the skilled artisan given the diversity of the receptor/ligand pairs, one skilled in the art would not expect that sequence variation in the extracellular portion of BMCA that binds Blys or BAFF would have the same binding and functional properties. Applicants also rely upon Moreland et al to teach pharmaceuticals comprising other TNF -related ligand/receptor pair. This is not persuasive, because the prior art requires a dimer in order to function *in vivo*. Therefore, success for one cannot ligand/receptor pair does not predict success with a different pair given that they target different biological activities and function differently as compared to other family ligand/receptor pairs. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). In view of the fact that the compounds have not been demonstrated to have the claimed activity in vitro and that the control of B cell activity is multifold and has duplicative cytokine activation mechanisms, the skilled artisan would be forced to make and test to see if one could use the invention is claimed. The courts have held that the disclosure is insufficient

when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* 153 USPQ 48 (CCPA 1967).

Rejections Maintained

Claims 19, 20, 25-27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising an isolated B cell activating factor receptor (BAFF-R) of SEQ ID NO: 1 or a fragment comprising residues 1-51 of SEQ ID NO: 1 that binds B cell activating factor (BAFF), wherein the BAFF-R is optionally fused to the Fc region of an immunoglobulin it does not reasonably provide enablement for sequence variants, naturally occurring variants, allelic variants, mammalian homologues or percent variants thereof and fusions to an immunoglobulin per se. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons made of record in the all the prior Office Actions and herein.

Applicants' arguments have been carefully considered but are not persuasive. Applicants essentially argue for the same reasons as set forth in the discussion of priority. The provisional document is not enabled for reasons set forth in the priority document. In contrast to Applicants statements of record, the examiner has stated reasons to do doubt the asserted truth of Applicants specification. Applicants argue that lack of demonstration of binding of the fragment comprising amino acids 8-41 of SEQ ID NO:1 is not basis for non-enablement of the claims because the specification teaches that amino acids 8-41 encompass the cysteine rich domain and Smith et al teach that the cysteine rich domain is "the canonicoal motif" of the TNF receptor superfamily. Smith et al teach that the canonical motif of all of the TNF receptors is that of cysteine-rich pseudorepeats, each containing about six cysteines and 40 amino acids. Smith et al admit that considerable variation and size and number is evident (Figure 1). The receptors of

Smith et al have multiple repeats. The claim is drawn to an apparently single motif. Applicants' arguments are not persuasive because there is no teaching in Smith et al that teaches that the "canonicoal motif" of 40 amino acids is the minimal ligand binding sequence of the extracellular domains. Further, even if the canonicoal motif provides for binding, a point that the examiner does not concede, the claims have sequence variation and the BMCA peptide does not have to have the argued cysteine-rich pseudorepeats that form the canonicoal motif of Smith et al. Applicants argue that the generation and screening of variants will not be undue and as such the rejection should be withdrawn. This is not persuasive because Applicants' have no written description for any of these other desirable compounds are not enabled for such and that applicants' are not entitled for dominance of further patentable inventions by claims that are insufficiently supported by the specification (*In re Fisher*, 166 USPQ 18, CCPA (1970)). The courts have held ".. in cases involving predictable factors, such as mechanical or electrical elements, a single embodiement provide broad enablement in the sense that once imagined, other embodiemnts can be made without difficulty and their preformance charactersistics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictably of factors involved." (In re Fisher 166 USPQ 18 (CCPA)). In the instant case the preformace characteristics of pharmaceutical and binding BAFF (SEQ ID NO:9) cannot be predicted by known scientific laws. The effect of any change of an amino acid cannot be predicted from known laws and can only be empirically determined. The art of record and relied upon in the office actions of record provide a plethora of evidence that similar structure does not predict similar function and function cannot be predicted from the mere primary sequence. The courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* 153 USPQ 48 (CCPA 1967). Further, applicants have not provided description and enablement of a representative number of species within the claimed

genus. See Angstadt, 537 F.2d at 502-03, 190 USPQ at 218". There is no guidance as to what changes can or cannot be made to the peptide. There is no guidance as to what residues are critical for binding. As such, the skilled artisan would be forced to discover these critical residues in order to make and use even a single variant within the claimed 95% genus. Applicants rely upon the incorrect standard of make and test to see if one could use without any expectation of success. The fact that not a single variant has been made, does not provide the skilled artisan with reasonable expectation that other variants could be made with routine experimentation as argued by Applicants. The issue is make and use and not make and test to see if you could possibly use. In the instant case, no variants have made and have been demonstrated to have any pharmaceutical effect *in vivo* or in fact bind BAFF *in vitro* or *in vivo*. Therefore, the skilled artisan would not have reason to believe that mere routine experimentation would reveal others that could be useful. Therefore, there is no expectation of success, the results of experimentation are highly unpredictable and therefore the argued experimentation is not routine. Applicants ague that the both the mouse and human sequences were known in the art at the time of invention and one skilled in the art could compare the sequences to determine substitutions and that Madry et al compare the sequence to define conserved regions and identify significant functional motifs. This is not persuasive because Madry et al does not define functional motifs. Madry et al does not teach that the mouse variant binds BAFF as claimed. Madry et al does provide the claim that BCMA is a new member of the tumor necrosis factor receptor superfamily, however it does not identify the ligand, nor does it identify binding domains. Applicants argue conservative variation of the polypeptide is likely to yield functional variants when the two sequences are compared. This is not persuasive because the claims are not limited to conservative variants. The teachings of Madry et al teach that the cysteine motif is conserved between the two species. The claims do not require this. Additionally the claims are not drawn to conservative variants as argued. Therefore, Applicants' arguments are not persuasive.

The rejection of claims 19, 20, 26, 27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50 and 52-56 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Gross et al (WO/00/40716, published 13 July 2000) is maintained for reasons made of record in the Office Action mailed 3-17-05.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that they are entitled to the priority date of provisional application 60/149,378 filed August 17, 1999. This is not persuasive, the provisional document lacks written description and is not enabled for reasons made of record above and is not enabled for the claimed invention reasons made of record herein.

The rejection of claim 25 under 35 U.S.C. 102(a) as anticipated by Gross et al (WO/00/40716, published 13 July 2000) is maintained for reasons made of record in the Office Action mailed 3-17-05.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that they are entitled to the priority date of provisional application 60/149,378 filed August 17, 1999. This is not persuasive because priority is not accorded this date in view of the lack of enablement for reasons set forth *supra*. For assignment of priority date for this claim, please see the office action of 3-17-05 that grants the PCT filing date for priority for this claim.

Claims 19, 20, 25, 26, 27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50 and 52-56 are rejected under 35 U.S.C. 102(e) as anticipated by Shu et al (U.S. Patent No. 6,475,987, issued November 5, 2000, filed May 5, 2000 with benefit of priority to May 1, 2000, provisional application 60/201,012).

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that they are entitled to the priority date of provisional application

60/149,378 filed August 17, 1999. This is not persuasive; the priority is not accorded in view of the lack of enablement of the provisional document for made of record above.

Claims 19, 20, 26, 27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50 and 52-56 are rejected under 35 U.S.C. 102(e) as anticipated by Shu et al (U.S. Patent Application Publication 2003/0148445 A1, published August 7, 2003, with benefit of priority to May 1, 2000, provisional application 60/201,012).

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that they are entitled to the priority date of provisional application 60/149,378 filed August 17, 1999. This is not persuasive because priority is not accorded in view of the lack of enablement for reasons set forth supra.

Status of Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645